PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 21978 PC INS	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/003285	International filing date *(day/month/year)* 08.03.2005	Priority date *(day/month/year)* 09.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/00 A61K31/454 A61K38/17 A61P1/16 A61K31/415		
Applicant INSERM		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.01.2006	31.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Hoff, P Telephone No. +31 70 340-3520

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/003285

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-28 as originally filed

   Claims, Numbers

   1-25 received on 18.01.2006 with letter of 18.01.2006

   Drawings, Sheets

   1/4-4/4 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 26,27
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6(partially),8(partially),11-14(partially),16(partially),18(partially),21-25(partially) and 16-25 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 16-25 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-6(partially),8(partially), 11-14(partially),16(partially),18(partially),21-25(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6,9,15,19,22-24
	No:	Claims	1-3,7,8,10-14,16-18,20-21,25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	16-25 (see separate sheet)

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Re Item III.

1. Claims 16-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Present claims 1-6,11-14,16,21-25 relate to a compound defined by reference to a desirable characteristic or property, namely "antagonist of the CB1 receptor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Furthermore, present claims 8 and 18 relate to an extremely large number of possible compounds (any N-piperidino-3-pyrazolecarboxamides). Support within the meaning of Article 6 PCT and disclosure within the meaning of 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (II), including the compounds of claims 9,10,19 and 20, to the nucleic acid sequence coding for a protein comprising SEQ ID NO:1 and SEQ ID NO:2, with due regard to the general idea underlying the present invention.

No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV.

This Authority considers that there are two inventions covered by the claims indicated as follows:

1. Claims: 1-6(partially),7-10,14(partially),16(partially),17-20,21-25(partially)
Use of an antagonist of the CB1 receptor, which is a N-piperidino-3-pyrazolecarboxamide derivative or a compound of formula II, in the manufacture of a composition for the treatment of hepatic diseases which result in hepatic fibrosis.

2. Claims: 1-6(partially),11-13,14(partially),15,16(partially),21-25(partially)
Use of an antagonist to any of the CB1 receptor variants defined in claims 12-14 (other than those of group 1) and a nucleic acid coding for said variants in the manufacture of a composition for the treatment of hepatic diseases which result in hepatic fibrosis.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem underlying the present application is to provide a medicament for the treatment of hepatic diseases which result in hepatic fibrosis.

The proposed solution is to use an antagonist of the CB1 receptor, in particular
1. a N-piperidino-3-pyrazolecarboxamide derivative or a compound of formula II
2. an antagonist to any of the CB1 receptor variants defined in claims 11-13 (other than those of group 1) and a nucleic acid coding for said variants

Where claims define chemical alternatives, unity of invention should be considered to be present when the alternatives are of a similar nature (PCT Guidelines, Chapt. 10, 10.17). Alternatives chemical compounds are to be regarded as being of a similar nature where:
(I) all alternatives have a common property or activity
and
(ii) a common structure is present, i.e. a significant structural element is shared by all of

the alternatives, or in case a common structure is absent, all alternatives belong to a recognised class of chemical compounds in the art to which the invention pertains.

The compounds of the present invention belong to a recognised group or a class of compounds which may be expected to behave in the same way in the context of the claimed inventions: the compounds of group 1 and 2 exhibit CB1 receptor antagonist activity.

This pharmacological property (CB1 antagonist), represents thus the technical feature which may, a priori, unify the different groups of compounds 1 and 2 of the present invention.

However, the use of CB1 receptor antagonists, including the N-piperidino-3-pyrazolecarboxamide SR141716(A), in the treatment of a hepatic disease which result in hepatic fibrosis such as liver cirrhosis has been already described in the state of the art. In this respect it is pointed out that liver cirrhosis is a hepatic disorder characterised by fibrosis. As mentioned in the description, cirrhosis is the end stage of many forms of liver injury characterised initially by fibrosis (page 1, lines 14-18).

US-A-5939429 discloses the use of a drug that selectively blocks CB1 receptors such as SR141716, for treating patients suffering from severe cirrhosis of the liver.

XP1120431 describes the pressor effect of SR141716 in cirrhotic rats and its potential clinical significance in the medical management of patients with advanced liver cirrhosis.

WO-A-03084930, WO-A-03084943, WO-A-03063781 and WO-A-087037 disclose the use of various CB1 receptor antagonists in the treatment of liver cirrhosis.

Consequently, because antagonists of the CB1 receptor (including SR141716) have been already disclosed for treating hepatic diseases characterized by fibrosis in the state of the art (see the various references mentioned above), this pharmacological property can no longer serve as a single general inventive concept linking the different groups of compounds 1 and 2 which have no other special technical features in common.

Therefore, the uses of the compounds 1 and 2 for the treatment of hepatic diseases represent each a distinct invention, characterised by its own special technical feature.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed below. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual group of compounds.

As the applicant has had a search report drawn up on the two inventions, the present opinion has been established on the basis of all parts of the international application.

Re Item V.

1 Reference is made to the following document:

D1: US-A-5 939 429 (SANYAL ARON ET AL) 17 August 1999 (1999-08-17)

D2: BATKAI S ET AL: "ENDOCANNABINOIDS ACTING AT VASCULAR CB1 RECEPTORS MEDIATE THE VASODILATED STATE IN ADVANCED LIVER CIRRHOSIS" NATURE MEDICINE, NATURE PUBLISHING, CO, US, vol. 7, no. 7, July 2001 (2001-07), pages 827-832, XP001120431 ISSN: 1078-8956

D3: GABBAY EZRA ET AL: "Treatment with an endocannabinoid antagonist improves neurological function and survival in an animal model of fulminant hepatic failure." HEPATOLOGY, vol. 38, no. 4 Suppl. 1, October 2003 (2003-10), page 541A, XP008033135 & 54TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES; BOSTON, MA, USA; OCTOBER 24-28, 2003 ISSN: 0270-9139

D4: WO 03/084930 A (SANOFI SYNTHELABO ; BARTH FRANCIS (FR);

MARTINEZ SERGE (FR); RINALDI-C) 16 October 2003 (2003-10-16)

D5: WO 03/084943 A (SANOFI SYNTHELABO ; BARTH FRANCIS (FR); MARTINEZ SERGE (FR); RINALDI-C) 16 October 2003 (2003-10-16)

D6: WO 03/063781 A (HAGMANN WILLIAM K ; QI HONGBO (US); MERCK & CO INC (US); SHAH SHRENIK) 7 August 2003 (2003-08-07)

D7: WO 03/087037 A (HAGMANN WILLIAM K ; LIN LINUS S (US); MERCK & CO INC (US); SHAH SHRENI) 23 October 2003 (2003-10-23)

D8: WO 2005/046689 A (SANOFI-AVENTIS; ARNONE, MICHELE; BENSAID, MOHAMMED; HERBERT, JEAN-MARC) 26 May 2005 (2005-05-26)

D9: WO 2004/058744 A (SANOFI-SYNTHELABO; MISCORIA, GILLES; RINALDI, MURIELLE; SCHOFIELD, JOS) 15 July 2004 (2004-07-15)

D10: WO 2004/007551 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; VU, HUY, KHANG; GROBLEWSKI, TH) 22 January 2004 (2004-01-22)

2 NOVELTY

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7,8,10-14,16-18,20-21,25 is not new in the sense of Article 33(2) PCT.

The document D1 discloses the use of a drug that selectively blocks CB1 receptors such as SR141716, for treating patients suffering from severe cirrhosis of the liver (hepatic disorder characterised by fibrosis).

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7,8,10-14,16-18,20-21,25 is not new in the sense of Article 33(2) PCT.

The document D2 describes the pressor effect of SR141716 in cirrhotic rats and its potential clinical significance in the medical management of patients with advanced liver cirrhosis.

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,11-14,16,21,25 is not new in the sense of Article 33(2) PCT. The documents D4,D5,D6 and D7 disclose the use of various CB1 receptor antagonists in the treatment of liver cirrhosis.

2.4 However, the subject-matter of claim 15 appears to be new and meets therefore the requirements of Article 33(2) PCT.
None of the available prior art documents discloses the use of a nucleic acid sequence coding for a protein comprising SEQ ID NO:1 and SEQ ID NO:2 for treating hepatic diseases which result in hepatic fibrosis.

3 INVENTIVE STEP

3.1 Should the Applicant have overcome the objections of lack of novelty raised above, an inventive step could not be acknowledged over D1 to D7 as the present subject-matter of claims 1-3,7,8,10-14,16-18,20-21,25, as far as novel, appears to be an obvious alternative over said documents (Article 33(3) PCT).

3.2 Furthermore, it is well established in the prior art that CB1 receptor antagonists are useful in the treatment of hepatic diseases characterised by fibrosis and more particularly in the treatment of liver cirrhosis (see D1 to D7).
The subject-matter of claim 15 therefore differs from those documents in that an other molecule capable of inhibiting the activation of CB1 receptor is used.

The solution proposed in claim 15 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

Document D10 discloses the nucleic acid and amino acid sequences of a variant cannabinoid 1 (CB1) receptor (the sequences of claim 15) and their use in the treatment or prevention of CB associated disorders. The polynucleotides encoding CB1 receptor, variants or fragment thereof may be used for therapeutic purposes to inhibit CB1 receptor activity (page 12, lines 10-21).

Consequently, being aware of the therapeutic activity of CB1 antagonists in the treatment of liver disorders which result in hepatic fibrosis (in particular liver cirrhosis), and knowing from D10 that the nucleic acid sequences coding for a protein comprising SEQ ID NO:1 and SEQ ID NO:2 inhibit CB1 receptor activity, the man skilled in the art faced with the problem of treating liver disorders characterised by fibrosis (cirrhosis) would have inevitably been led to use the nucleic acid of claim 15 to solve the problem posed.

3.3 Dependent claims 4-6,9,19,22-24 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1 to D7 and the corresponding passages cited in the search report.

4 INDUSTRIAL APPLICABILITY

4.1 There are no doubts about industrial applicability for the subject-matter of claims 1-15 (Art.33(4) PCT).

4.2 For the assessment of the present claims 16-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI.

1. The PCT application WO2005/046689 (D8) which describes the use of the CB1 antagonists rimonabant and N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide for treating hepatic diseases such as non-alcoholic steatohepatitis is relevant for novelty for the subject-matter of claims 1-2,5,7-10,14,16-

20,23,25.

2. The PCT application WO2004/058744 (D9) which describes the CB1 antagonist N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide and its use in the treatment of liver cirrhosis is relevant for novelty for the subject-matter of claims 1-3,7-9,14,16-19,21,25.

The priorities of the conflicting applications have however not been checked.